Prostate Cancer Proceedings

Meeting to Discuss Prostate Cancer Screening and the Role of Public Health

Invitational by the Utah Department of Health
January 7, 2003

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Summary of Proceedings

The Utah Department of Health sponsored a meeting on January 7, 2003, to discuss issues related to prostate cancer screening, review the current guidelines and revise, as needed, the recommendations made in 1995 for public and private practitioners. Twenty-three individuals representing primary care, urology, oncology, public health, the insurance industry, the Utah Cancer Registry, medical ethics, and the American Cancer Society attended the meeting.

The meeting was divided into three sessions. In the first session, six speakers presented facts about prostate cancer and screening. During the second session, the participants were divided into two groups to discuss the role of public health in prostate cancer screening and to review the 1995 prostate cancer meeting recommendations. In the third session, the participants developed recommendations for future action.

The presenters highlighted several key points during the first session. First, prostate cancer results in significant morbidity and mortality. Second, there are potential benefits as well as potential risks associated with prostate cancer screening. Third, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, a large, randomized clinical trial sponsored by the National Cancer Institute, is still underway; results regarding prostate cancer screening outcomes will not be available for another five years. Therefore, clinicians and patients need up-to-date information in order to make educated decisions about screening.

During the second session, issues related to prostate cancer screening were discussed. These included the fact that screening increases awareness about a significant health problem and might result in a cure for individuals. Conversely, disadvantages of screening included the morbidity associated with diagnostic and therapeutic procedures and the lack of data on whether early detection prolongs life and/or improves the quality of life. Participants discussed the need for improved access to educational materials that would facilitate informed decision-making by providers and patients.

Recommendations from Proceedings

During the final session, the group unanimously opposed the development of a statewide, population-based prostate cancer screening program and the direct provision of prostate cancer screening services by Utah's public health agencies (the Utah Department of Health and Utah's Local Health Departments). In addition, the large group agreed that the Utah Department of Health should:

- Develop a regularly updated, electronic source of accurate information about prostate cancer screening issues for providers and the general public
- Develop a strategy to increase the number of men 40 years of age or older who make regular visits to a health care provider to receive appropriate preventive services, which may include prostate cancer screening
- Seek to assure access to appropriate prostate cancer screening services to uninsured and high-risk groups as well as encourage Utah's private and public health insurance plans to voluntarily comply with a resolution passed by the 2001 Utah Legislature which includes prostate cancer screening as a covered benefit
- Provide information annually about prostate cancer screening issues and progress related to the above recommendations to the participants at the proceedings meeting who will serve as members of an ad hoc prostate cancer screening advisory group in the future

Introduction

Public and private practitioners are often required to make decisions with insufficient data and whether or not to screen for prostate cancer is one such situation. For this reason, it is not surprising that professionals may have different points of view. Therefore, the Utah Department of Health sponsored a meeting on January 7, 2003 to provide a forum in which to discuss issues related to prostate cancer screening, review the screening guidelines developed at a Department sponsored meeting in March 1995, and develop recommendations for future action. Twenty-three individuals representing primary care, urology, oncology, public health, the insurance industry, the Utah Cancer Registry, medical ethics, and the American Cancer Society attended the meeting. For a list of attendees, please see Appendix A.

The meeting was divided into three sessions. In the first session, six speakers presented facts about prostate cancer and screening. During the second session, the participants were divided into two groups to brainstorm about the role of public health in prostate cancer screening and review the 1995 prostate cancer meeting recommendations. In the third session, the participants regrouped in order to develop recommendations for future action.

Session One: Presentation by Speakers

Please see Appendix B for a list of the key points made by each of the six speakers at the meeting.

Session Two: Discussion of Issues Related to Prostate Cancer Screening

During the second session, the participants were divided into two groups to discuss the role of public health in prostate cancer screening. Additionally, the conclusions and recommendations of the March 1995 prostate cancer proceedings meeting were reviewed and discussed. The summaries of each group are presented below. In general, the groups raised many of the same issues and reached similar conclusions.

Group 1

The participants in this small group session felt that there was not enough evidence at the present time to warrant prostate cancer screening as part of population-based screening programs.

Group members also felt that men should be encouraged to have conversations with their health care providers about their overall health and not only about prostate cancer screening. All men in the appropriate age group and not just the men in high risk groups should be encouraged to have this conversation with their providers. The group also felt that populations/families at high risk for developing prostate cancer needed to be identified.

Group members emphasized that educational materials for both the physician and the public need to be developed. In fact, education of the public may be the most important role that public health can play regarding the issue of prostate cancer screening. While the group members agreed that a message to consumers about prostate cancer screening needs to be developed, a consensus was not reached regarding the content of that message.

Group II

Members of this group also felt that there was not enough evidence at the present time to revise the conclusion reached in 1995 stating that public health should not include prostate cancer screening as part of a population-based screening program. The example given to justify this position was the use of routine mammography in the detection of breast cancer and the scientific evidence that exists to support such screening. In contrast, group members felt that there was not sufficient evidence to endorse mass screening of all males for prostate cancer at the present time.

Group members also expressed the need for increased availability of educational materials for both providers and patients. Patients contemplating PSA testing need accurate information in order to make an informed decision. This information needs to include the costs and benefits (pros and cons) of screening. As medical information is constantly changing, providers and patients both need to be up-to-date regarding the latest evidence-based medical practices. Additionally, there needs to be an awareness of physician bias related to screening and treatment.

Some methods for providing this education were mentioned including the creation of a table that could illustrate (1) overall mortality vs. morbidity and (2) the negative effects of screening and possible increase of morbidity. Another method mentioned was the development of an educational script or video. Members agreed that educational materials needed to be available on the Internet.

Members of this group felt that problems remain regarding the accuracy of the PSA test. It was mentioned that there are alternative tests such as the DRE, which may be able to detect other health issues. Like the members of Group I, participants in Group II also felt that health education for men should be addressed using a holistic approach rather than focusing specifically on prostate cancer screening.

Members of this group were concerned about current access to screening services and treatment for men in high-risk groups such as African American men, men with a family history of prostate cancer, and men age 50 or older. Members felt that overall health assessment of men considered to be at high risk for prostate cancer should be encouraged.

Session Three: Development of Recommendations

During the final session, the group unanimously opposed the development of a statewide, population-based prostate cancer screening program and the direct provision of prostate cancer screening services by Utah's public health agencies (the Utah Department of Health and Utah's Local Health Departments). In addition, the large group agreed that the Utah Department of Health should:

- Develop a regularly updated, electronic source of accurate information about prostate cancer screening issues for providers and the general public
- Develop a strategy to increase the number of men 40 years of age or older who make regular visits to a health care provider to receive appropriate preventive services, which may include prostate cancer screening
- Seek to assure access to appropriate prostate cancer screening services to uninsured and high-risk groups as well as encourage Utah's private and public health insurance plans to voluntarily comply with a resolution passed by the 2001 Utah Legislature which includes prostate cancer screening as a covered benefit
- Provide information annually about prostate cancer screening issues and progress related to the above recommendations to the participants at the proceedings meeting who will serve as members of an ad hoc prostate cancer screening advisory group in the future

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Appendix B: Speaker Presentations

Chuck Wiggins, Ph.D.
Director, Utah Cancer Registry

Dr. Wiggins presented data about the incidence and mortality of prostate cancer in Utah. Listed below are some of his key points:

- The Utah Cancer Registry is a population-based registry and has been a member of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program since 1973.

- Prostate cancer is the most commonly occurring cancer in Utah men.

- 1,300 new cases of prostate cancer and 200 deaths from this cancer were estimated to occur in Utah during 2002.

- A dramatic increase in the incidence of prostate cancer was seen in Utah during the years 1990 through 1992. Since then, the rate have declined but remain higher than they were prior to 1990.

- Annual age-specific incidence rates of prostate cancer were presented for both Utah and the U.S. during the period 1973-2000. While Utah's rates showed greater variability, the trends in Utah over time appeared to mimic those seen for the U.S. With the exception of men age 80 and older, all age groups appeared to experience an increase in incidence rates for prostate cancer over time. This increase appeared to be greatest for men in the 40 to 49 and 50 to 59 year age groups.

- Annual age-specific mortality rates of prostate cancer were also presented for both Utah and the U.S. during the period 1973-2000. While Utah's rates showed greater variability, the trends in Utah over time appeared to mimic those seen for the U.S. The rates for men in the 50 to 59, 60 to 69, 70 to 79, and 80+ age groups appeared to experience a slight decline in mortality rates in recent years. The mortality rate for U.S. men age 40 to 49 remained flat. There were too few deaths among Utah men aged 40 to 49 during this time period to calculate stable rates.

- The annual age-adjusted incidence rates for prostate cancer by stage of disease at the time of diagnosis were presented for the U.S. for the period 1973 through 2000. The incidence rates were substantially higher for cases detected at the summary local/summary regional stages compared to cases detected at the summary distant stage. Therefore, the increase in incidence rates that has been seen nationally over time has largely been due to the detection of earlier stage disease.

- The percentage of U.S. prostate cancer cases diagnosed at the summary local/ summary regional stages increased over the time period from 1973 through 1999. Approximately 60% of cases were diagnosed at the local or regional stage in 1973. This percentage increased to about 90% of cases in 1999.

Ray M. Merrill, Ph.D., M.P.H.
Brigham Young University

- Dr. Merrill summarized information regarding risk factors and the potential benefits and risks of screening for prostate cancer. Listed below are some of his key points:

- Suspected risk factors for prostate cancer include increasing age, African American race, high fat diet, obesity, certain environmental exposures, vasectomy, benign prostatic hypertrophy, certain sexually transmitted diseases, a family history of prostate cancer and genetic factors.

- Potential benefits of screening for prostate cancer include the fact that, according to some experts, early detection saves lives and may avert future cancer-related illness for some men. Screening also results in the detection of earlier pathologic stages at which cancer may be treated.

- For screen detected cases, aggressive treatment with radical prostatectomy or radiation therapy potentially adds three more years of life for men in their 50s, 1.5 years for men in their 60s, and 0.4 years for men in their 70s.

- Potential risks of screening for prostate cancer include the occurrence of minor, self-limiting complications that have been reported in as many as 40% of men who have had biopsies.

- Other potential risks include the fact that patients who undergo radical prostatectomy face greater than a 50% chance of permanent sexual dysfunction, 20% to 30% likelihood of some degree of chronic urinary incontinence, and a 0.5% chance of operative death. Radiotherapy is generally associated with lower risk for these adverse effects but has about a 10% chance of causing bowel dysfunction.

- Limitations of the digital rectal exam include the fact that the area of the prostate that is available for physical exam is limited to the peripheral zone.

- Limitations of the prostate specific antigen or PSA test include the fact that it is not specific, that is, an elevated PSA may result from benign prostatic hyperplasia, acute prostatitis, transrectal needle biopsy, acute urine retention, transurethral resection of the prostate (TURP), and possibly ejaculation.

- Dr. Merrill described a current research project in which he and others sought to determine whether the comparatively high incidence rates for prostate cancer among white men in Utah represent higher rates among members of The Church of Jesus Christ of Latter Day Saints, and whether screening for prostate cancer likely explains any differences in the rates for LDS and non-LDS men.

- According to study results, LDS men had a 27% higher incidence rate of prostate cancer compared to non-LDS men during the study period.

- Prostate cancer incidence rates for local/regional disease were higher for LDS men compared to non-LDS men. In contrast, the rates for distant disease were lower for LDS men compared to non-LDS men.

- According to the Utah Health Status Survey, a statewide survey conducted in 1996, a higher percentage of LDS men compared to non-LDS men reported receiving a PSA test in the past year. This trend was seen across all age groups: men 50 to 59 years of age, men 60 to 69 years of age, and men 70 years and older.

Robert Stephenson, M.D.
Endowed Chair, Department of Urology
University of Utah State Dept. of Health

Dr. Stephenson spoke about treatment for prostate cancer and presented outcomes data. Listed below are some of his key points:

SEER Prostate Cancer Data Mortality

- Gradual increase in mortality rates in the U. S. from 1973 to 1991, the peak year
- Leveling off of mortality rates from 1991-1993
- 19.5% decline in mortality from 1991-1998
- Mortality declines are statistically significant
- Other studies: Tyrol, Quebec, Boyle

Percent Mortality Declines by Year Percent Decline from:		
Year	**Previous Year Peak**	**Peak Year (1991)**
1992	0.4%	0.4%
1993	0.8%	1.1%
1994	2.3%	3.4%
1995	3.9%	7.1%
1996	3.2%	10.1%
1997	5.8%	15.4%
1998	4.9%	19.5%

U.S. Prostate Cancer Mortality Statistically significant mortality declines are now observed:

- In both younger (<65) and older (65 and over) men
- Whites and blacks
- Mortality declines are generally accelerating

The Paradox of PSA Era Prostate Cancer

- Fewer men are dying of prostate cancer as a result of PSA mediated early detection and treatment
- However, these declines in mortality are quite small when compared to the large numbers of men diagnosed and treated with prostate cancer
- These findings also suggest increases in over-diagnosis and treatment
- Over-diagnosis and over-treatment: concurrent with the successful life saving efforts of diagnosis and treatment we are achieving in some men, we are also treating many men who do not need treatment, men destined to die of other causes of death

Prostate Cancer: The Challenge of Correct Decision-making

- Mortality data have the precision of hindsight
- Date of death and interval from diagnosis to death are precisely known. Cause of death is also well attributed.
- At the time of cancer diagnosis the date of death and cause of death are matters of very weak statistical speculation for individual patients

- The dilemma: making the correct treatment decision for an individual patient with woefully inadequate tools
- No tools available for the precise determination of time to death in individual patients from non-prostate cancer causes -- The Mack truck problem
- No precise tools for determining the time to death from prostate cancer
- Until both determinations are precisely made there will always be over-treatment and/or under-treatment

Conservative vs. Aggressive Treatment for Prostate Cancer
- Conservative strategies result in under-treatment of patients who will benefit
- Aggressive strategies result in over-treatment of patients who do not need therapy
- Both are correct strategies, but only some of the time
- Better methods of determining length of life and time to prostate cancer death will improve this situation, but not by much
- Life will continue to be a very uncertain proposition, particularly when considering a disease of prolonged natural history in mature men

Randomized Trial of RRP vs. WW - NEJM
- Comparison RRP vs. Watchful Waiting
- 695 men – localized prostate cancer
- Median follow-up 6.2 years
- Mean PSA, Gleason score, stage similar
- CaP deaths: 31 WW vs. 16 RRP (p=0.02)
- Death any cause: 62 WW vs. 53 RRP (p=0.31)
- Metastasis: 54 WW vs. 35 RRP (p=0.03)

Effect of Hormone Therapy on Prostate Cancer – Messing Trial
- 98 men, all were N+ after RRP
- Randomized to WW vs. early hormone therapy
- Median follow-up 7.1 years
- Free of disease at last follow-up including undetectable PSA: 77% in early hormone group vs. 18% in WW
- 43% alive and free of disease in WW group, 77% alive and free of disease in early hormone group
- 31% died of CaP in WW group, 6% died of CaP in the early hormone therapy group

Effect of Hormone Therapy on Prostate Cancer – Bolla Trial
- 412 patients randomized to XRT vs. XRT + 3 yrs hormone therapy
- 80% T3, most with high PSA, high grade
- 5 year overall survival: 62% XRT alone, 78% XRT + hormones
- PSA progression free survival: 40% XRT alone, 74% XRT + hormones

Kermit Heid
Prostate cancer survivor
Facilitator of the Utah Chapter of the American Cancer Society's support group, Man to Man

Mr. Heid is an advocate of prostate cancer screening. Listed below are some of the key points from his presentation:

Trends in Prostate Cancer:

- Five-year survival rates have increased dramatically during the Prostate Specific Antigen (PSA) era that began circa 1990: 1974-1976: 67%; 1992-1998: 97%. *American Cancer Society Facts and Figures 2002 and SEER Data, Table XXII-2.*
- Nationally, the 1992 death rate was 39.1/100,000 men (all ages, all races) whereas the 1999 death rate was 31.1/100,000 men – a 20.5% reduction in only 7 years!! *SEER Data, Table XXII-3.*
- According to Judge Ralph Burnett, former chairman of the National Prostate Cancer Coalition, before the advent of PSA testing nearly 75% of men diagnosed with prostate cancer were in the late stages of the disease. The introduction of PSA testing has resulted in 75% of today's diagnoses being early or localized stages. According to the American Cancer Society, treatment of localized prostate cancer results in a 5 year survival rate of nearly 100% compared to a 33% 5 year survival rate for late stage disease.
- If PSA screening is started at the age of 50, annual or biannual PSA alone is highly efficient to identify the men who are at high risk of having prostate cancer. F. Labrie, et al, *Prostate, February 1, 1999.*
- Rates of over diagnosis of prostate cancer by PSA screening are low. For white men, only about 15% were diagnosed with cancer that would not have been clinically detected in their lifetime. Dr. Laurie Barclay, *Medscape Medical News, 3 July 2002.*

Cost and Benefit of Prostate Cancer Screening:

- The cost per year of a life saved with PSA and DRE screening was $3,574 to $4,627 for men aged 50-69 while the cost per year of a life saved with PSA alone was $3,822 to $4,956 for men aged 50-70 years. R. M. Benoit, et al, *Prostate Cancer and Prostatic Diseases, Vol. 4, 2001, pp 138-145.*

Legal Actions:

- To date, 26 states have enacted laws requiring insurers to include coverage for PSA testing.
- Prostate Cancer Malpractice Cases: According to a Long Beach Community Cancer Center study, of 22 plaintiff awards totalling over $8.4 million, roughly $7.5 million could have been avoided if PSA screening and diagnostic guidelines had been followed.

Future Trends in Screening:

- *Remember, screening = diagnosis, not treatment.*
- More extensive use of PSA velocity and PSA density, as well as other variations on the original PSA test will become more common.
- The use of color Doppler and tissue harmonic ultrasound will also be used more extensively.
- Physicians may be able to order less frequent tests depending on the PSA level.
- Magnetic resonance spectroscopic imaging may be used to identify aggressive prostate tumors and cancers that have spread beyond the prostate.

Summary:

- Utah has the 9th highest incidence of prostate cancer among 44 states reporting and the majority of those with higher rates are southern states with a higher African-American population.
- The mortality rate appears to be declining since the introduction of PSA testing.
- The age-specific incidence in the 40-59 year age group is increasing and, according to one Veteran's Administration source, younger men's cancers tend to be more aggressive.
- Since the introduction of PSA testing, localized and not distant disease is the norm at the time of diagnosis. The result appears to be a decline in mortality rates even while incidence rates are increasing.

An Advocate's Recommendations:

- In 2003, 200 men in Utah are estimated to die of prostate cancer.
- It appears PSA testing has reduced mortality rates and Utah should embrace such testing.
- We should aggressively pursue outreach and education programs for all Utah men.
- We should pursue means to screen and treat underserved and underprivileged men similar to the current breast cancer screening and treatment programs that are currently in place in Utah.

Ian Thompson, M.D.
University of Texas Health Sciences Center
San Antonio, Texas

Dr. Thompson prepared a video tape in which he explored the question, "Early Diagnosis of Prostate Cancer: Should we offer screening?" Some of the key points from his presentation included the following:

- Major differences exist in the screening recommendations of various medical specialty organizations.
- Some of the concerns mentioned regarding screening for prostate cancer included the possible detection of tumors of no biologic significance, length time bias, cost of screening, morbidity resulting from screening/biopsy/treatment, and lack of proven efficacy.
- Two clinical trials are ongoing to determine whether screening reduces mortality from prostate cancer: the PLCO trial in the U.S. and the Rotterdam trial in Europe.
- There is also evidence of the benefit of screening: results of a "worst case" analysis of 337 men who underwent radical prostatectomy revealed that fewer than one in seven tumors were insignificant.
- There is evidence that complication rates from treatment of prostate cancer with radical prostatectomy are falling.
- A decrease in prostate cancer mortality has been observed nationally (in SEER and Department of Defense data), as well as in Canada and Austria. A similar decrease has not been observed in Mexico (where PSA screening is not performed).
- Screening appears to be finding tumors early that can be cured. Screening also appears to be saving lives.
- Screening for prostate cancer should begin at age 50. Screening should begin at an earlier age for high-risk populations: African Americans and individuals with a family history of prostate cancer.
- There are three options from which to choose regarding screening. The first option is to deny screening, with the result that some men are denied the benefit of screening. Option two is to mandate screening for all men. This option is probably inappropriate as some men will be treated unnecessarily and this will increase costs. Option three is to offer screening to all at risk. The last option has the advantage of allowing individual decision-making.
- Offering screening allows an individual man's priorities to determine whether or not to undergo screening. Everyone is different: some men will want to be screened and others won't. Who's right? They all are.
- It becomes our responsibility [health care providers and the public health community, among others] to educate the public.

Saundra Buys, M.D.
Professor of Medicine
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The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial is a 10-site randomized controlled study sponsored by the NCI. Subjects are men and women between 55 and 74 years of age at entry, and are randomized to receive either screening for cancer or usual care which may or may not include cancer screening, depending on the physician's recommendations. Screening for prostate cancer includes yearly PSA for 6 years and yearly digital rectal exam for 4 years. The primary objective is to determine if screening for these cancers reduces site-specific cancer mortality. Using mortality as an endpoint is crucial in cancer screening trials because surrogate endpoints, such as cancer stage and survival, introduce biases (including overdiagnosis bias and length bias) that may support screening even if mortality is not impacted.

The first patients were enrolled in 1994. Enrollment is complete, with 154,000 subjects randomized. Approximately 37,000 men have been randomized to the screened group. The University of Utah (including the St. Luke's Hospital in Boise, which is a Utah satellite center) has enrolled 13,000 subjects. Outcome data for prostate cancer will not be available for another 5 years. Some of the observations to date are as follows:

- The benefit of screening for prostate cancer is still unknown. A few years ago an international prostate cancer consortium ranked the PIVOT trial as the most important ongoing trial of prostate cancer, and PLCO as the next most important. The PIVOT trial randomized men diagnosed with prostate cancer to "intervention" vs "observation." If it is not clear that treating prostate cancer improves mortality, it is certainly not clear that diagnosing prostate cancer through screening will improve mortality. The PLCO trial is a trial of screening alone, and no specific treatment algorithm is mandated.

- Although the benefit of screening is unknown, men who choose to undergo PSA screening may not all need to have yearly screens. The PSA value at baseline is a strong predictor of subsequent years' values. For example, men with PSA less than 1 have a very low likelihood of developing an abnormal PSA in the next several years, and repeat screening at 5 years may be reasonable. Similarly, screening men with PSA from 1-2 every 2 years would miss very few abnormal values and would result in a cost savings over yearly screens.

- Contamination and compliance are both major factors in cancer screening trials. Contamination refers to the subjects in the control arm who receive screening, and ideally is very low. Compliance refers to the subjects in the screened arm who receive screening and ideally is very high. The eligibility criteria were changed after the pilot phase to reduce the problem of PSA contamination in the control arm.

- Ascribing cause of death can be another major confounder. For example, a man with known prostate cancer who dies is likely to have "prostate cancer" listed as the cause of death, even if the death is not directly due to prostate cancer. A "death review committee" within PLCO, which is blinded to the arm of the trial to which the patient was randomized, is responsible for determining the cause of death.